

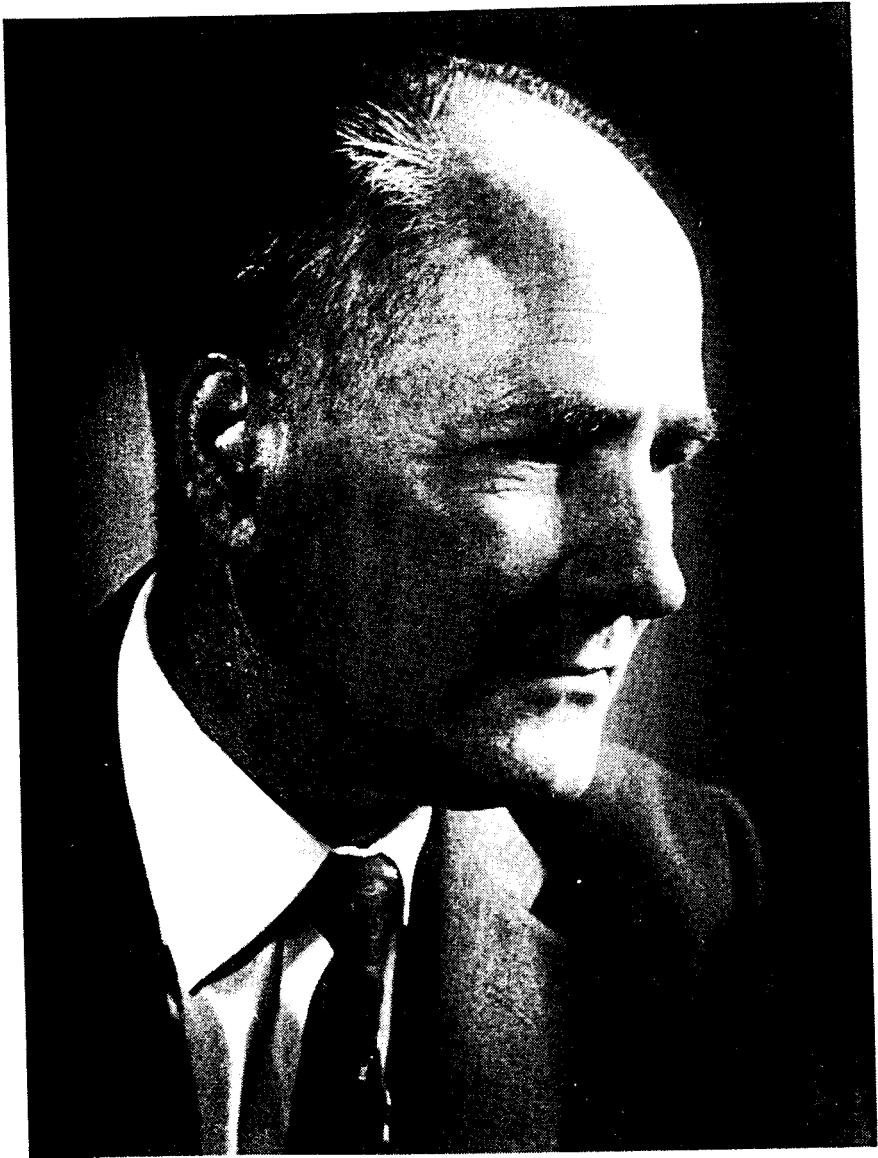
Beadle ↓

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W. W. Leaden

GEORGE WELLS BEADLE*

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BY N.H. HOROWITZ

*Division of Biology, 159-29, California Institute of Technology,
Pasadena, California 91125, U.S.A.*

GEORGE WELLS BEADLE was born to Hattie Albro and Chauncey Elmer Beadle in Wahoo, Nebraska, on 22 October 1903. He died in Pomona, California, on 9 June 1989. Beadle was one of the giant figures of genetics in our time. He initiated the series of great discoveries made between 1941 and 1953 that brought to a close the era of classical genetics and launched the molecular age. For this achievement, he received many honours, including the Nobel Prize. Beadle also had a distinguished career as an academic administrator. When he retired in 1968, he was President of the University of Chicago. He never lost his love of experimental genetics, however, and after his retirement he resumed experimental work on a favourite subject: the origin of maize. In 1981, he gave up research because of increasing disability from the Alzheimer's disease that eventually ended his life.

Beadle – his oldest friends usually called him by his boyhood nickname, 'Beets' – grew up on his father's 40 – acre farm near Wahoo. The farm was a model for farms its size and was so designated by the U.S. Department of Agriculture in 1908. Beets's mother died when he was four years old, and he and his brother and sister were raised by a succession of housekeepers. As a boy, he worked on the farm, and he retained for the rest of his life the skills he learned as a gardener and beekeeper, and the handiness with tools. Gardening remained one of the great pleasures of his life, almost to the end. During the war, the Victory Garden he grew around his home at Stanford provided enough produce for two families. It included beehives, but Beets wouldn't eat the honey because, he said, he had been stung too many times as a boy. On the other hand, he loved corn and raised several kinds, including a small Mexican variety that gave his garden the distinction of having the earliest sweet corn at

*This memoir has appeared in *Genetics*, the *Biographical Memoirs* of the National Academy of Sciences and the *American Philosophical Society Year Book*.

Stanford. After his retirement to Pomona in 1982, he derived much pleasure from growing flowers. He pursued this hobby until he was no longer able to find his way to his garden and back again.

Beets did well in school and was inspired by high-school science teacher Bess MacDonald (to whom he more than once acknowledged a debt in later years) to go on to college. Despite his father's opinion that a farmer didn't need all that education, he entered the University of Nebraska College of Agriculture in 1922. He graduated in 1926 with a B.S. degree and stayed on for another year to work for a master's degree with Franklin D. Keim. His first scientific publication was with Keim and dealt with the ecology of grasses. At some point along the way, under Keim's beneficial influence, Beets became interested in fundamental genetics and was persuaded to apply to the graduate school at Cornell University instead of going back to the farm. He entered Cornell in 1927 with a graduate assistantship and shortly afterward joined R.A. Emerson's research group on the cytogenetics of maize. Corn genetics was new and exciting for Beets, and Emerson and the people around him (they included Barbara McClintock and Marcus Rhoades) were inspiring. The result was that in the following five years, he published no fewer than 14 papers dealing with the investigations on maize that he began at Cornell while a graduate student.

In 1928, he married Marion Hill, a graduate student in botany at Cornell, who assisted him with some of his early corn research. Their son, David, was born in 1931.

Beets received his Ph.D. in 1931 and was awarded a National Research Council Fellowship to do post-doctoral work at the California Institute of Technology in T.H. Morgan's Division of Biology. At Caltech, Beadle began to do research on *Drosophila*; at the same time he finished the work on maize cytogenetics that he had started at Cornell – specifically, on genes for pollen sterility, sticky chromosomes, and failure of cytokinesis, and on chromosome behaviour in maize-teosinte hybrids. The last was a subject he would return to in his retirement, after he had been away from research for many years. Out of it would come one of the most interesting investigations of his career.

His *Drosophila* studies at Caltech were concerned with the results of crossing over within various chromosomal rearrangements. Among the most important of these was a study with Sterling Emerson of crossing over in attached-X chromosomes, which showed that exchanges occur at random between any two non-sister chromatids. Another investigation, reported jointly in a large paper with A.H. Sturtevant, was the first systematic study of crossing over and disjunction in chromosomes carrying inversions. E.B. Lewis has described this paper as 'monumental'. Both papers are classics of their type.

In 1934, Boris Ephrussi arrived at Caltech from Paris to learn some *Drosophila* genetics from Morgan and Sturtevant. He was just two years older than Beadle, and they became close friends. His interest was in the problem of gene action, a subject in which he soon interested Beadle. Ephrussi was skilled in the techniques of tissue culture and transplantation, and he and Beadle planned a collaborative study on *Drosophila* utilizing these methods. In mid-1935, the two men went to Paris to carry out the experiments in Ephrussi's laboratory at the Institut de Biologie. Their attempts to grow imaginal discs in tissue culture failed, but they devised a method for transplanting discs from one larva to another, where the disc continued to develop. Before the year's end, they had gone as far as they would be able to go with this methodology, and they had worked out a hypothesis to account for the interaction they observed in transplanted flies between the genes *vermilion* and *cinnabar*. They showed that the results could be explained by the following assumptions:

(i) the normal alleles of the two genes control the production of two specific substances, called the v^{+} - and cn^{+} -substances, both necessary for brown eye-pigment formation; (ii) the v^{+} -substance is a precursor of the cn^{+} -substance; and (iii) gene mutation blocks formation of the corresponding substance. It did not become clear until much later that the two substances are actually chemical precursors of the brown pigment, and the two authors frequently referred to them as 'hormones'.

None of this seems like much by modern standards, but it was a great advance at the time. It suggested that development could be broken down into series of gene-controlled chemical reactions, an idea that cried out for further investigation; and it implanted in Beadle the germ of the one-gene-one-enzyme idea that he later brought to full flower. But first the two eye-colour substances had to be identified. The identification took five years. By that time, Beets was hunting for bigger game.

Following his return from Paris, Beadle moved to Harvard University as an assistant professor. During his stay there, he was met on a few brief occasions by the young woman who later became my wife. She remembered him fondly afterwards as the only member of the Harvard faculty who spoke to Radcliffe undergraduates at biology departmental teas.

Beadle left Harvard the following year (1937) for Stanford University, where he had accepted an appointment as professor of biology. He was joined by biochemist Edward L. Tatum (1909–1975) as a research associate; Tatum contributed his skills to the work of isolating and identifying the two eye-colour substances. They spent the next three years on this problem. They, with others, established that the two substances are derivatives of tryptophan, and by 1940 Tatum had obtained a crystalline preparation of the v^{+} -substance. They were beaten to the identification, however, by Butenandt, Weidel and Becker who adopted the simple procedure of testing known metabolites of tryptophan for their biological activity. They found that kynurenine is active as the v^{+} -substance and, later, that OH-kynurenine is active as the cn^{+} -substance. Much later it was shown that the brown pigment is formed from two molecules of OH-kynurenine.

Despite this setback in the laboratory, the years from 1937 to 1939 were not wasted for Beadle. During this period, he joined A.H. Sturtevant in writing a superlative textbook, *An Introduction to Genetics*, published in 1939. J.A. Moore has called this book 'the complete statement of classical genetics'.

As a result of his *Drosophila* experience, it became clear to Beadle that an entirely different method would be needed to make headway with the problem of gene action. No other non-autonomous traits were known in *Drosophila*, and the autonomous ones – of which there were many – were of such towering complexity from the biochemical standpoint that it was hopeless to attempt to reduce them to their individual chemical steps. Beets enjoyed telling how the solution to this problem came to him while he was listening to a lecture by Tatum in a course the latter was giving on comparative biochemistry. Microbial species, Beets learned, differ in their nutritional requirements, despite the fact that they share the same basic biochemistry. If these differences are genetic in origin, he thought to himself, it should be possible to induce gene mutations that would produce new nutritional requirements in the test organism. If successful, such an approach would yield genes governing known biochemical compounds immediately, rather than genes for unknown substances requiring years to identify, as was the case with almost all then-known mutations.

What was needed for such an undertaking was an organism that was genetically workable and that could be grown on a chemically defined medium. Beadle knew just the organism.

He had heard about *Neurospora crassa*, the red bread mould, while he was still a graduate student at Cornell. B.O. Dodge had come to the campus from the New York Botanical Garden to give a lecture on *Neurospora*, and Beets remembered the lecture clearly. It dealt with the genetics of the organism and included results on first- and second-division segregations of the mating-type and other loci. Even years later Beets was still pleased to recall that he and some other graduate students were able to convince the sceptical Dodge that his data could be explained by crossing over, or the lack of it, between the gene and its centromere.

Dodge had an important role in the history of *Neurospora*. It was he who discovered that the ascospores could be germinated by heat, thus closing its life cycle and making the organism accessible for genetic study. He also did basic studies on its genetics and was enthusiastic about its possibilities for genetic research. He convinced T.H. Morgan, who was a friend, to take some cultures with him to Pasadena when, in 1928, Morgan went out there to found the Division of Biology at Caltech. According to Beadle, Dodge told Morgan that *Neurospora* would be 'more important than *Drosophila* some day'. In Pasadena, Morgan assigned the cultures to a graduate student, Carl Lindegren, to work on for his thesis in genetics. Lindegren studied the relation between first- and second-division segregations and crossing over. He completed his thesis in 1931, the year Beadle arrived at Caltech.

The question of the nutritional requirements of *Neurospora* was still an open one in 1940. Previous workers had used nutrient agar as the growth medium, but this would not do for the experiment Beadle had in mind. It was known that related fungi had simple requirements, however, and Tatum soon showed that *Neurospora* grew on a synthetic medium containing sugar, salts and a single growth factor, biotin. This medium was thenceforth referred to as 'minimal medium'. Fortunately, purified concentrates of biotin had recently become available. Nothing now stood in the way of an experimental test of Beadle's idea.

The final step was to clear the *Drosophila* cultures out of the Stanford lab and convert it into a laboratory for *Neurospora* genetics. The plan was to x-ray one parent of a cross and collect offspring (haploid ascospores isolated by hand) onto a medium designed to satisfy the maximum number of possible nutritional requirements (so-called 'complete medium'). The resulting cultures would next be transferred to minimal medium. Growth on complete medium, combined with failure to grow on minimal medium, was to be taken as presumptive evidence of an induced nutritional requirement. The requirement would be identified, if possible, and the culture would be crossed to wild type to determine its heritability.

Given the climate of the time, the scheme was breathtaking in its daring. There was still a suspicion among non-geneticists that genes governed only trivial biological traits, such as eye colour and bristle pattern. The really important characters were determined in the cytoplasm, by some unknown mechanism. Even among geneticists, there was a widespread belief that gene action was far too complex to be resolved by any simple experiment. Indeed, the outcome of their trial run was so uncertain that the two investigators agreed at the outset to test 5000 ascospores before giving up the project; and to avoid early disappointment, they isolated and stored over a thousand spores before testing any of them.

Success came with spore no. 299, which gave rise to a culture that grew on complete medium, but not on minimal unless it was supplemented with pyridoxine. This mutant was followed by others showing requirements for thiamine and p-aminobenzoic acid, respectively. All three requirements were inherited as single-gene defects in crosses to wild type. These mutants were the subject of the first *Neurospora* paper by Beadle and Tatum

(1941). Before long, mutants requiring amino acids, purines and pyrimidines were also found. The science of biochemical genetics had been born.

Beadle knew that he and Tatum had discovered a new world of genetics and that more hands would be needed to explore it. He came to Caltech early in the fall of 1941 to give a seminar on the new discoveries and to recruit a couple of research associates to join the enterprise. The seminar was memorable. The first Beadle – Tatum paper on *Neurospora* had yet to be published, and no-one in the audience had an inkling of what was to come. I recorded my recollection of it in an article published in honour of Beadle's 70th birthday:

The talk lasted only half an hour, and when it was suddenly over, the room was silent. The silence was a form of tribute. The audience was thinking: nobody with such a discovery could stop talking about it after just 30 minutes – there must be more. Superimposed on this thought was the realization that something historic had happened. Each one of us, I suspect, was mentally surveying, as best he could, the consequences of the revolution that had just taken place. Finally, when it became clear that Beadle had actually finished speaking, Professor Frits Went – whose father had carried out the first nutritional studies on *Neurospora* in Java at the turn of the century – got to his feet and, with characteristic enthusiasm, addressed the graduate students in the room. This lecture proved, said Went, that biology is not a finished subject – there are still great discoveries to be made!

David Bonner and I accepted appointments with Beadle and joined his group at Stanford the following year. Later, H.K. Mitchell and Mary Houlahan (Mitchell) came. There were also graduate students (including A.H. Doermann and Adrian Srb) and a steady turnover of visitors in the lab. The next four years were the most exciting of my life. I imagine that the same was true for everyone else in the lab. Before the *Neurospora* revolution, the idea of uniting genetics and biochemistry had been only a dream with a few scattered observations. Now, biochemical genetics was a real science, and it was all new. Incredibly, we privileged few had it all to ourselves. Every day brought unexpected new results, new mutants, new phenomena. It was a time when one went to work in the morning wondering what new excitement the day would bring.

Beadle presided over this scientific paradise with the enthusiasm, intelligence and good humour that characterized everything he did. He was a popular and much admired boss. He worked in the lab with everyone else. He especially enjoyed working with his hands, and he had plenty of opportunity to indulge himself in this regard. The laboratories were located in the basement (the 'catacombs') of Jordan Hall, a location that gave them a certain remoteness from the campus. There was a bench and lathe in the lab, and Beets used these to make small equipment and do minor repairs around the place; he called the campus shops only for major work. Actually, he did anything he had time for. I came to work early one morning and found him painting one of the rooms. All this was in addition to his research and his teaching duties as a professor of biology. He always did more than anyone else. I recall a lab picnic on a summer day at the beach, over the coast range of hills from the Stanford campus. To save gas, we bicycled, huffing and wheezing (we had no gears then). The only difference between Beets and the rest of us was that he was carrying a watermelon on his handlebars.

Beets knew his responsibilities and took them seriously. It was wartime, and he had to concern himself with all that this implied for the pursuit of fundamental research. He had to find financial support for the programme, and he had to try to keep his group together. He succeeded on both scores. He obtained support from both the Rockefeller Foundation and the Nutrition Foundation; this support lasted through the war and was continued afterwards. In

addition, the *Neurospora* programme was classified as essential to the war effort by the Committee on Medical Research of the Office of Scientific Research and Development. No senior researcher or, as I recall, graduate student was drafted, although some of us were called up for physical examinations. The *Neurospora* research had obvious practical applications of potential utility in the war effort. One of these had to do with the development of bioassays for vitamins and amino acids in preserved foods, and another with a search for new vitamins and amino acids. We worked on both these applications during the war years, although the major thrust of the lab remained basic science. Toward the end of the war, Beadle was asked by the War Production Board to devote part of the effort of the lab to seeking mutants of *Penicillium* with increased yields of penicillin. He complied, of course, but we were not successful in this endeavour.

The biochemical and genetic studies carried out between 1941 and 1945 on *Neurospora* mutants in the Stanford laboratory showed that the biosynthesis of any given substance of the organism is under the control of a set of non-allelic genes. Mutation of any one of these genes results in loss of the synthesis, due to blocking of a single step in the biosynthetic pathway. In 1945, Beadle summarized the whole field of biochemical genetics in an historic article in *Chemical Reviews*. Here, he proposed that the biochemical actions of genes could be explained by assuming that genes are responsible for enzyme specificity, the relation being that 'a given enzyme will usually have its final specificity set by one and only one gene. The same is true of other unique proteins, for example, those functioning as antigens.' This statement became known as the 'one gene-one enzyme' hypothesis of gene action. It is Beadle's major legacy to fundamental genetics. Controversial at first, it was eventually demonstrated to be correct. (The controversy is itself an interesting reflection of the state of genetics at the time.) Important though this summary statement of the *Neurospora* findings is in the history of science, there is little doubt that Beets's most inspired contribution to genetics was the method he devised with Tatum to produce the mutants from which the theory was derived. He showed how lethal mutations could be recovered by the use of a micro-organism with known nutritional requirements. As Tatum later found, the same method could be applied to bacteria. Using the resulting mutants, Tatum's student, Joshua Lederberg, demonstrated genetic recombination in *E. coli* and thereby founded modern bacterial genetics. Beadle, Tatum and Lederberg shared the Nobel Prize in 1958.

In 1945, with the war drawing to a close, the team of Beadle and Tatum dissolved when Tatum departed Stanford for Yale University. In the following year, Beadle returned to Caltech – this time to succeed T.H. Morgan as chairman of the Division of Biology. Morgan had died, and there was a need to find as his successor a first-rate biologist who would continue the Morgan tradition – that is, strong emphasis on experimental, quantitative and chemical biology. (Since the beginning of the Biology Division at Caltech, biochemistry had been included in it.) Beadle was the ideal choice. It is interesting that the key figure in the negotiations on the Caltech side was the chemist, Linus Pauling. Pauling had a lively interest in the new genetics, understood its importance and later made important contributions to it. It is doubtful that Beadle would have made the move to Caltech had it not been for Pauling's intercession. For a time after returning to Caltech, Beets continued with laboratory research, but administrative matters began to absorb his attention and finally swallowed him up. He stopped working in the lab. His last research paper on *Neurospora* was published (with H.K. Mitchell and J.F. Nyc) in 1947. After that, and for the next 30 years, his scientific writings consisted of reviews, lectures, historical essays and a prize-winning book for young people,

The Language of Life: An Introduction to the Science of Genetics. The book was co-authored with his second wife, Muriel Barnett, a writer, whom he married in 1953 following his divorce. (Muriel had a son, Redmond, by her deceased husband; he became Beadle's son by legal adoption.)

In an autobiographical sketch published in 1974, Beets made the following revealing statement about his decision to give up laboratory research:

In my own situation, I tried a quarter of a century ago what I thought of as an experiment in combining research in biochemical genetics with a substantial commitment to academic administration. I soon found that, unlike a number of my more versatile colleagues, I could not do justice to both. Finding it increasingly difficult to reverse the decision I had made, I saw the commitment to administration through as best I could, often wondering if I could have come near keeping up with the ever increasing demands of research had I taken the other route. My doubts increased with time.

He finally did, in fact, come back to research – after his retirement – as will be seen.

Beadle fulfilled the expectations of him as successor to the legendary Morgan. This can be seen in the faculty appointments made during his tenure as chairman. These included Max Delbrück, Renato Dulbecco, Ray Owen, Robert Sinsheimer and Roger Sperry. Aside from the eminence of the names, these appointments set the directions of the post-war growth of the Biology Division toward molecular, cellular and behavioural biology. The division has followed them ever since. In addition, the material wealth of the division increased considerably during Beadle's tenure. Not the least of the additions were two new laboratory buildings.

Beets was later described as a chairman who steered the division without actually seeming to run it. He was informal, unaffected and open. At the same time, he was hardheaded and witty. His insights were often expressed in memorable quips. My favourite of these – one that I like because it is true and because it is pure, unmistakable Beadle – says 'It's hard to make a good theory – a theory has to be reasonable, but a fact doesn't.' I quoted it with great effect at a meeting on the origin of life held in Moscow in 1957. When I got back to Pasadena, I told Beets about it. As usual, he couldn't remember saying it.

In 1961, Beadle left Caltech to become President of the University of Chicago. Why he took this job and what he did after he arrived in Chicago were for years a mystery to me and, I suspect, to most if not all of his old scientific friends. Everybody who visited the university at that time knew that it was in trouble because of urban decay in the surrounding neighbourhood, and a little later everyone heard about the spectacular student sit-ins, but none of this seemed to connect with the George Beadle we knew.

The mystery was cleared up in 1972, four years after Beadle's retirement, with the publication of a book by Muriel Beadle entitled *Where Has All The Ivy Gone?* This book is an honest and highly entertaining account of the Beadles' years at the University of Chicago. It explains why the university wanted Beets as its president (to restore its academic standing after difficult years which saw the loss of many first-class faculty members), why he took the job (it was put to him as a challenge by a persuasive Dean of the Law School, Edward Levi, who later succeeded Beadle as president), and what he did there (a great deal).

Friends of mine at the university have informed me that Beadle was much admired as president and that he did staunch the loss of faculty, notably in the sciences and medicine. He is remembered by many for the garden he established on the campus, near the president's

house, where he could be observed at work in the early morning. Some were surprised later to discover that this man was the president of the university. They thought he was a hired gardener.

In 1968, Beadle attained mandatory retirement age. He and Muriel decided to remain in Chicago, and they bought a home in Hyde Park, one of the neighbourhoods saved by the urban renewal programme they had both worked hard on. Now Beets returned to research, after 23 years in the wilderness. The problem he chose to investigate – the origin of maize – was one he was familiar with from his Cornell days. Maize is a cultivated plant that cannot survive in the wild. How did it arise? R.A. Emerson and Beadle showed that it is closely related genetically and cytologically to teosinte, a plant that grows wild in Mexico and Guatemala. They considered teosinte the most plausible ancestor of maize. In 1939, Beadle found that teosinte seeds – which are enclosed in a hard coat that makes them inedible – can be popped, like ordinary popcorn. This, he pointed out, would have given prehistoric Americans an incentive to grow teosinte as a food plant from which they could have selected the mutations that, in time, transformed it into maize.

This theory was criticized by Paul Mangelsdorf, the most important objection being that there was little archaeological evidence to support it. In its place he proposed that maize evolved from a hypothetical wild corn, now extinct. Beadle decided in his retirement to gather more evidence on the question. In this undertaking he displayed the same vigour and inventiveness that distinguished the researches of his younger days. He summarized his findings in a lecture he delivered at Caltech in 1978 on the occasion of the fiftieth anniversary of the founding of the Biology Division. In this brilliant *tour de force*, he touches on every aspect of the subject: genetics, linguistics, palynology, archaeology, folklore, animal behaviour. (What does a squirrel do when given seeds of maize and teosinte?) He describes an experiment on himself to decide whether teosinte meal is edible. He is informative, witty and persuasive. His conclusion is unambiguous: 'Just when and where the American Indians transformed teosinte into corn we do not know, but it was surely the most remarkable single plant-breeding achievement of all time.' This must have been one of Beets's last public lectures. As a finale to a scientific life, it could hardly have been better.

George Beadle has passed into history now. His papers are rarely read any more, his lively presence is no longer felt, but the changes he brought about in biology are permanent. No scientist could ask for a grander memorial than that.

HONOURS AND DISTINCTIONS

Honorary Degrees

Doctor of Science

- 1947 Yale University
- 1949 University of Nebraska
- 1952 Northwestern University
- 1954 Rutgers University
- 1955 Kenyon College
- 1956 Wesleyan University
- 1959 Birmingham University
- 1959 Oxford University
- 1961 Pomona College

1962 Lake Forest College
1963 University of Rochester
1963 University of Illinois
1964 Brown University
1964 Kansas State University
1964 University of Pennsylvania
1966 Wabash College
1967 Syracuse University
1970 Loyola University, Chicago
1971 Hanover College
1972 Eureka College
1973 Butler University
1975 Gustavus Adolphus College
1976 Indiana State University

Legum Doctor (LL.D.)

1962 University of California, Los Angeles
1963 University of Miami
1963 Brandeis University
1966 Johns Hopkins University
1966 Beloit College
1969 University of Michigan

Litterarum Humaniorum Doctor (L.H.D.)

1966 Jewish Theological Seminary of America
1969 DePaul University
1969 University of Chicago
1969 Canisius College
1969 Knox College
1971 Roosevelt University
1971 Carroll College

Director of Public Services

1970 Ohio Northern University

Awards

1950 Lasker Award
1951 Dyer Award
1953 Emil Christian Hansen Prize (Denmark)
1958 Albert Einstein Commemorative Award in Science
1958 Nobel Prize in Physiology or Medicine (with E.L. Tatum and J. Lederberg)
1959 National Award, American Cancer Society
1960 Kimber Genetics Award

- 1967 Priestley Memorial Award
- 1967 Edison Prize, Best Science Book for Youth (with Muriel Beadle)
- 1972 Donald Forsha Jones Medal
- 1984 Thomas Hunt Morgan Medal

Professional and Honorary Societies

Genetics Society of America (President, 1945), American Association for the Advancement of Science (President, 1955), National Academy of Sciences (Council, 1969–1972), American Philosophical Society, American Academy of Arts and Sciences, Royal Society, Danish Royal Academy of Sciences, Japan Academy, Instituto Lombardo di Scienze e Lettere (Milan), Genetical Society of Great Britain, Indian Society of Genetics and Plant Breeding, Indian Natural Science Academy, Chicago Horticultural Society (President, 1968–1971), Phi Beta Kappa, Sigma Xi.

ACKNOWLEDGEMENT

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BIBLIOGRAPHY

The complete bibliography appears on the accompanying microfiche. A photocopy is available from the Royal Society Library at cost.